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Clinical applications of anginin in ophthalmology. I. A case of the arteriosclerotic retinopathy with the retinal venous thrombosis favorably treated with anginin, especially effects of anginin on white sheating of the retinal artery

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Abstract

A case of arteriosclerotic retinopathy associated with retinal venous thrombosis was treated with Anginin and the following results obtained: 1) Visual acuity was improved from 0.03 to 0.7. 2) Retinal hemorrhages were absorbed and pipe-stem sheathing of the branch of retinal artery decrease, with white sheathing remaining partially. 3) It was therefore considered that the pipe-stem sheathing was decreased because Anginin removed venous spasm and improved the blood stream of the branch of the artery, and that the organic changes already established on the arterial wall would remain as white sheathing. 4) Anginin could not prevent retinal veins from changing into white lines. 5) Consequently the authors considered that Anginin may be a drug effectively used for retinal arteriosclerosis and retinal venous thrombosis associated therewith.

CLINICAL APPLICATIONS OF ANGININ IN OPHTHALMOLOGY

I. A CASE OF THE ARTERIOSCLEROTIC RETINOPATHY WITH THE RETINAL VENOUS THROMBOSIS FAVORABLY TREATED WITH ANGININ, ESPECIALLY EFFECTS OF ANGININ ON WHITE SHEATHING OF THE RETINAL ARTERY

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Anginin is an atoxic pyridine derivative having a structure of 2, 6-pyridine dimethanol bis (N-methyl carbamate) and specifically inhibits stasis, enlargement of endothelial gaps at the outset of venules and increase in permeability of blood vessels which result from venous spasm caused by kinin. It is an agent of anti-hemorrhagic, anti-thrombotic, anti-inflammatory and anti-atherosclerotic action, whose therapeutic effect on various diseases has already been reported^{6, 8, 11, 18~26, 28~31}.

The authors who have been investigating the therapeutic effect of Anginin in ophthalmology, could obtain an ophthalmoscopic finding suggestive of improved blood stream in the branches of retinal artery together with increased visual acuity as well as improved findings of ocular fundus from the use of the drug in a case of arteriosclerotic retinopathy associated with retinal venous thrombosis, which are discussed in the following.

CASE REPORT

Patient: A 64-year-old female

First examination: Feb. 22, 1965

Chief complaint: Visual disturbance of right eye

Present history: The patient suddenly became aware of visual disturbance, especially defect of upper visual field of right eye 2 days previously without any inducement.

Present condition: Ocular findings: Visual acuity is 0.03 (n. c.) for the right and 1.0 (n. c.) for the left. No abnormality is observable in the anterior part of the eyes and intermediate vitreous body.

In right ocular fundus, disc of the optic nerve is well demarcated and in normal color but a broad fan-shaped hemorrhage along retinal inferior temporal

vein ranging about 2 disc diameters distant from disc of the optic nerve to the periphery is observed together with white patches seen at places within the hemorrhagic focus. Hemorrhage is observed in macular area too. Reflex of the blood-column of retinal artery is remarkably increased presenting a picture of copper-wire arteries. At the arterio-venous crossings are seen crossing-phenomena such as nicking, banking, tapering and humping. The caliber of retinal artery is found to be irregular, with small blood-spots observed at places around the blood vessel in the peripheral region of the retina.

In left ocular fundus, disc of the optic nerve is well demarcated and in normal color but reflex of the blood-column of retinal artery is increased and crossing-phenomena including nicking, tapering and humping are observed together with the irregularity of arterial caliber. No hemorrhage nor white patch is observed.

General findings : Both build and nutrition are moderate. There is no abnormal ECG finding. Blood pressure 196/94 mm Hg; amount of hemoglobin 11.2g/dl; number of red cells 3,910,000; white cell count 6,300; thrombocyte count 133,000; bleeding time 1 min. 30 sec.; coagulation time from 3 min. 30 sec. until 11 min. after bleeding; staff neutrophils 2 %; segmented neutrophils 44%; lymphocytes 44; eosiophils 4 %; monocytes 6 %; basophils 0 %; serum cholesterol 212 mg/dl; no abnormality in urine.

Diagnosis : Arteriosclerotic retinopathy of right eye with retinal branch thrombosis of inferior temporal vein (Keith-Wagener Group II, Scheie arteriosclerosis degree III, hypertension degree III).

Retinal arteriosclerosis of left eye (Keith-Wagener Group II, Scheie arteriosclerosis degree II, hypertension degree II).

Treatment and course of condition : Medication consisted of oral administration of Kallikrein 30 u., Hesna 3.0g, Rutin C 1.0g, ϵ -aminocaproic acid 3.0g, intravenous injection of 20% glucose, vitamin C 100mg and Kativ 100 mg and subconjunctival injection of hypertonic saline solution, while Polyregulon 3mg and Beniol 3 tablets were given orally in cases of hypertension as necessary in reference to blood pressure.

Blood pressure fell down to maximum 140~150 mm Hg and minimum 70~80mm Hg since May, but findings of ocular fundus of right eye were hardly improved. Visual acuity of right eye remained to be 0.05 (n. c.) in August when retinal hemorrhage was being absorbed a little. Subsequent oral administration of Anginin 6 tablets (250mg in each tablet) was started on Sept. 8 in combination with oral administration of Hesna 3.0g and Rutin C 1.0g and subconjunctival injection of hypertonic saline solution brought about remarkable absorption of retinal hemorrhages in right eye towards the end of Sept. Fig. 1 represents a finding of ocular fundus of right eye on Sept. 29, in which obsolete

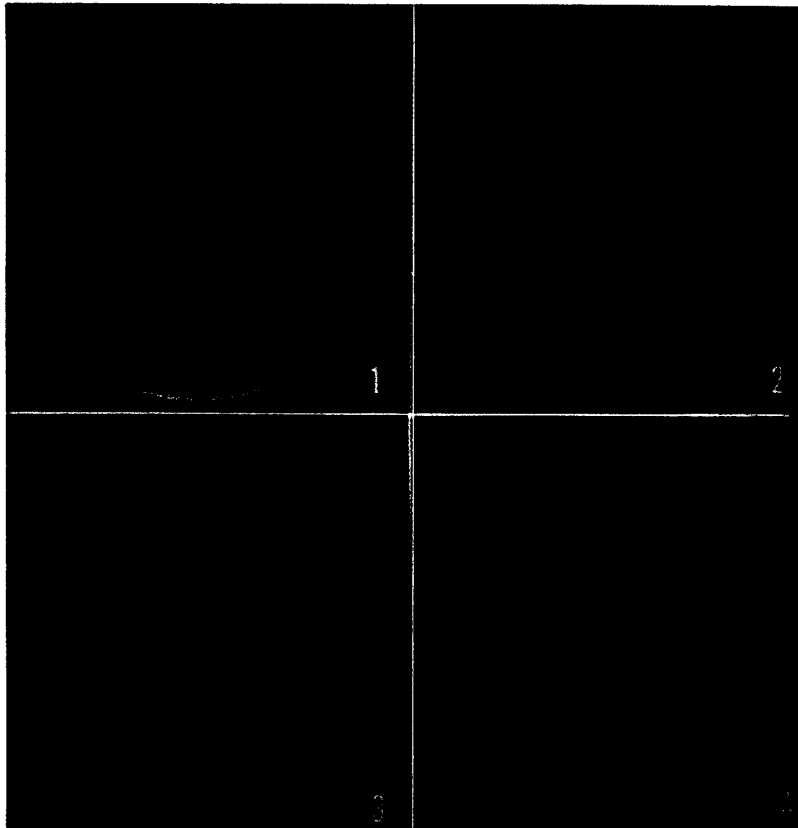


Fig. 1 Fundusphotograph of right eye on Sept. 29, in which retinal hemorrhages, white patches, change of veins into white lines and remarkable arterio-venous crossing phenomena are seen. Marked narrowing of caliber and significant white sheathing or pipe-stem sheathing are noticeable in the branch of retinal inferior temporal artery (arrows).

Fig. 2 Fundusphotograph on Oct. 6. The arterial branch of somewhat increased caliber is seen as partial white sheathing on arterial wall, suggesting improved circulation therein (arrows).

Fig. 3 Fundusphotograph on Oct. 13. The caliber of a branch of retinal inferior temporal artery is further increased, with white sheathing observed only partially, suggesting further improvement in the blood stream in the branch (arrows).

Fig. 4 Fundusphotograph on Oct. 27. An evidence of blood stream being maintained in the branch of retinal inferior temporal artery (arrows).

retinal hemorrhage, white patches, change of veins into white lines and remarkable arterio-venous crossing phenomena are seen. Marked narrowing of caliber and significant white sheathing or pipe-stem sheathing are noticeable in the branch of retinal inferior temporal artery, which shows that the branch is about to change into white line (arrows).

A finding on Oct. 6 is illustrated in Fig. 2, where improvement is seen in the branch of the artery that was about to change into white line, although no change is observed in the arterio-venous crossing phenomena or change of veins into white line: the branch of somewhat increased caliber is seen as partial white sheathing on arterial wall, suggesting improved circulation therein (arrows).

Fig. 3 represents a finding on Oct. 13: The caliber of a branch (arrows) of retinal inferior temporal artery is further increased, with white sheathing observed only partially, suggesting further improvement in the blood stream in the branch. However, there was no change both in the vein changed into white line and in arterio-venous crossing phenomena, while vascularization was observed in the region in which the crossing-phenomena occurred. Retinal hemorrhages were considerably absorbed and visual acuity recovered to 0.3 (0.3 x + 1.0 D) for the right and 1.0 (n. c.) for the left.

Fig. 4 illustrates a finding on Oct. 27: Retinal hemorrhage in posterior pole was almost completely absorbed, an evidence of blood stream maintained in the branch of retinal inferior temporal artery (arrows).

In Dec. blood-spots were further absorbed, only a little remaining in the peripheral region of ocular fundus and visual acuity also recovered to 0.5 (n. c.) for the right and 1.0 (n. c.) for the left.

Consequently, subconjunctival injection was discontinued since Jan., 1966, the dose of Anginin was decreased to 4 tablets since Feb., and oral Anginin in this daily dose was continued singly since March when oral Hesna and Rutin C were also discontinued. Now in July, 1966, there is no remarkable change observed in the picture of white sheathing of the branch of retinal inferior temporal artery as well as of other arterial branches, nor any fresh retinal hemorrhage seen. Visual acuity has also been as high as 0.7 (n. c.) for the right and 1.0 (n. c.) for the left. However, venous branches more peripheral than arterio-venous crossing point which was about 2 disc diameters distant from disc of the optic nerve were changing since Feb. into white lines and became complete white lines towards the end of March. No side effect was observed.

SUMMARY AND DISCUSSION

This case was included in Group II of Keith-Wagener's classification, since there were arteriosclerosis, irregularity of caliber of arterioles as well as venous

thrombosis observed remarkably, while no obvious finding of angiospastic retinopathy such as cotton-wool patches was obtained in this case³².

Treatment consisted initially of uses of hypotensives, various hemostatics and subconjunctival injection of hypertonic saline solution together with Kallikrein. However, retinal hemorrhages began to be absorbed only after 6 months, with visual acuity remaining still unimproved. Therefore, Anginin having anti-Bradykinin action was started. It is said that Kallikrein liberates kinin,^{16,17} that administration of the drug may cause recurrence of auricular fibrillation normalized by Anginin²⁰ and that no improvement in symptoms was observed in occlusive diseases of the artery of the extremities under treatment with Anginin combined with Kallikrein.¹¹ Consequently, Anginin was used in combination not with Kallikrein but with Hesna, Rutin C and hypertonic saline solution injected subconjunctivally.

Retinal hemorrhages were remarkably absorbed 22 days after start of oral Anginin therapy. A detailed observation of blood vessels in the retina of right eye that became possible revealed remarkable narrowing of caliber of the branches of retinal inferior temporal artery as well as the so-called pipe-stem sheathing or arterial blood-column hidden completely by white sheathing over a considerable area. However, blood-column was still observed at the ends of the arterial branch changed into white line. This was considered to suggest that the change into white line might not be completed, with blood stream still maintained to some extent. Subsequent observation was made mainly in terms of the way in which the pipe-stem sheathing of the branch of retinal inferior temporal artery undergoes change by Anginin.

One week later or 29 days after start of oral Anginin, white sheathing of the branch subsided and appeared to be partial white sheathing with disappearance of the pipe-stem sheathing. Observation has been made for 10 months after start of oral Anginin therapy, which is even now being continued. The very white sheathing of branches of retinal inferior temporal artery did not progress but decreased with absorption of retinal hemorrhages and improvement in visual acuity. However, it did not disappear completely: it remained almost unchanged since 3 months after start of oral Anginin, persisting as an attendant line for the blood column of the artery.

Retinal artery turns into arterioles at the surface of disc.^{3,15} It is said that sclerotic lesion of retinal artery consists mainly of hyalinoidosis mainly including thickening of subendothelial basement membrane and that surrounding muscle cells as well as of fibrosis involving thickening of vessel wall due to proliferating muscle cells and increased fibrous structure, and more frequently, of fibrohyalinoidosis or fibrosis complicated by hyalinoidosis.^{4,13,15}

White sheathing of retinal artery is one of the findings of severe arterio-

sclerosis. HIWATARI³ pointed out severe thickening of the endothelium and mesothelium, significant proliferation of collagen fibers and connective tissues and considerable narrowing of vessel cavity due to proliferated endothelial cells. SUGANUMA¹⁴ stated that the blood vessel changes into white line if vessel cavity is obliterated by thickened endothelium: BALLANTYNE¹ that white sheathing appears when proliferated endothelium undergoes lipid degeneration: and KOYANAGI¹⁰ that white sheathing is caused by proliferation of connective tissue in periarterial exothelium. IZUKA,⁷ quoting a literature by Adam, stated that an attendant line for the artery in arteriosclerosis represents cellular or connective tissue proliferation of the endo- or exothelium. IKUI⁴ and MIMATSU,¹⁸ although not referred to white sheathing, wrote that a tendency for endothelial cell to retrogress with the progress of sclerosis was observed but not any picture of proliferation nor lipid degeneration of retinal vessels. More recently, KIMURA⁹ electron-microscopically observed thickened arterial wall, atrophied and diminished muscle cells, increased substances in basement membrane and abnormally proliferated glia, rich in fibers, in retinal artery that changed into white line.

As discussed above, much remains still unknown as to the histological picture of white sheathing of retinal artery. Based on the opinions of previous investigators as well as Ikui's detailed electron-microscopic study on retinal artery, the pictures seem to involve proliferation of periarterial gliocytes in addition to fibrohyalinoidosis including thickening of basement membrane, homogenization and anucleation of proliferated muscle cells and increased fibrous structure. It is improbable that such severe organic changes in the arterial wall or white sheathing should disappear in a limited period of time by administration of Anginin.

According to SHIMAMOTO,^{21,22} kinin causes venous spasm and hence stasis, which, in turn, widens venules or leaking vessels and enlarges their endothelial gaps. Anginin specifically inhibits the venous spasm caused by kinin. BURCH *et al.*² stated that kinin is formed more vigorously and produced kinin is harder to decompose in case of a state of hypoxia present in the downstream of an artery stenosed due to sclerosis. The authors² found that Anginin inhibits diminution of the oscillatory potential of the electroretinogram in albino rabbit caused by injection of Bradykinin in carotid, and presumed that the former may improve circulatory disturbance of the retina caused by the latter.

What was observed by the authors ophthalmoscopically as pipe-stem sheathing or the branch of retinal inferior temporal artery changed into white line seems to be brought about by organic changes and also circulatory disturbance in the branch of that artery which lay to the up stream of venule affected with convulsions caused by kinin which was formed in the downstream of the

sclerosed artery. It may be considered that the organic lesion of arterial wall which had already occurred persisted almost unchanged ophthalmoscopically as partial white sheathing in the branch involved, although a picture of pipe-stem sheathing disappeared in a relatively short time because of venous spasm removed by Anginin and blood stream in the branch of the artery improved. It is interesting to note that white sheathing of retinal inferior temporal vein was progressive and not inhibited by Anginin which proved to have an observable action to improve or prevent that of retinal arterial branches.

Anginin was experimentarily confirmed by SHIMAMOTO *et al.*²⁵ to strongly prevent edematous response of the artery and have a significant anti-atherosclerotic action, and pointed out to prevent cerebral arteriosclerosis.^{18,19,20,24} TAKAHASHI²⁶ stated that Anginin was clinically effective against cerebral arteriosclerosis. TANAKA *et al.*,²⁹ treating with Anginin, observed fibrinoid necrosis of cerebral arterioles but increased activity of dehydrogenase in arteriolar wall and no massive hemorrhage in rabbit with renal hypertension by Goldblatt's method.

Since little atherosclerosis has been observed in retinal arterioles,⁴ it depends upon further investigation whether Anginin has preventive action on the pathogenesis of sclerosis of retinal artery as of the artery of other tissues. IMAI⁶ and TAKAHASHI²⁷ found, however, edematous swelling of the artery as an initial change in arteriolosclerosis of the retina in choline deficient rat. Being presumed that kinin participates in the edematous swelling, Anginin may be considered to have preventive effect on the pathogenesis of arteriosclerosis of the retina.

Adjustment of blood stream in retinal artery, prevention of change of the artery into white line and absorption of retinal hemorrhage, attributable to the inhibition of venous spasm by Anginin were observed ophthalmoscopically by the authors this time. Anginin may be considered to be useful in retinal arteriosclerosis and retinal venous thrombosis associated therewith.

CONCLUSION

A case of arteriosclerotic retinopathy associated with retinal venous thrombosis was treated with Anginin and the following results obtained :

- 1) Visual acuity was improved from 0.03 to 0.7.
- 2) Retinal hemorrhages were absorbed and pipe-stem sheathing of the branch of retinal artery decrease, with white sheathing remaining partially.
- 3) It was therefore considered that the pipe-stem sheathing was decreased because Anginin removed venous spasm and improved the blood stream of the branch of the artery, and that the organic changes already established on the arterial wall would remain as white sheathing.
- 4) Anginin could not prevent retinal veins from changing into white lines.

- 5) Consequently the authors considered that Anginin may be a drug effectively used for retinal arteriosclerosis and retinal venous thrombosis associated therewith.

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